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EXAMINER
BERCH, MARK L

ART UNIT	PAPER NUMBER
1624	

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12

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/859,503	MCKENNON ET AL.	
	Examiner	Art Unit	
	Mark L. Berch	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 September 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 4-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 4-7, 18-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. The "benzamidyl" on last line of page 65 is not a carbocycle, and indeed, it is not at all clear what it is. A carbocycle is a ring with just carbons present, period. It is not clear what this "benzamidyl" is, but it appears to have N present. It could be an amidine or an amide, to which a phenyl or a benzyl group is attached, or it could even be a benzimidazolyl group, which is not a carbocyclic group but is a heterocycle. Applicants need to draw what this group is, and explain why one of ordinary skill in the art would be able to figure out that this is what is intended. But please note that a group of the form X-Y-, where X is a carbocycle, and Y is some linker, is not a carbocycle; it is a Y group substituted by a carbocycle. Deletion is suggested. The traverse is unpersuasive. Applicants have settled on the radical derived from benzamide. However, that is not "benzamidyl", but is instead "benzamido". Note the Hackh's reference, page 106 to this effect. Further, while it is

correct that the benzene ring is a carbocycle, this group is not the benzene ring. It is a nitrogen, attached to which is a carbonyl, attached to which is a benzene ring, and thus the benzamide group is not a carbocycle, but an amino group which is substituted by a moiety which contains a carbocycle.

2. The second step is unclear in claim 19; it is not consistent with the preamble either. The claim is a method of inhibiting, but the last step is not an inhibition step, but "determining." Does determining mean measuring the inhibition after it has occurred? Or is it just the mental step of observing that the inhibition has occurred or what? For example, suppose that the cytokine inhibits all the cellular processes, i.e. the cell inside someone's body dies, and suppose that the observer does not notice that this one cell has died. The preamble seems to have been met; the activity was inhibited, but step (b) isn't met because the cell death is unnoticed. Would that fall within the claim or not? The traverse is unpersuasive. Applicants explain what the word "determining" means. That is not the problem. The problem is the inconsistency with the preamble, which the response does not address. The "determining" is a purely mental act, and is the last step, yet the preamble calls for a physical act.
3. The phrase "cellular process or activity" is unclear. What is the difference between process and activity? Isn't every activity a process and vice versa? Is applicant using some specialized meaning of "process" that is somehow different from "activity"? Applicants' response is not understood. In terms of a cell, something going on, and being active, mean exactly the same thing. If a cell is active, it means that something is going on. If something is going on in the cell, that means that it is active. In other

words, activity in a cell means that a cellular process is going on. If applicants disagree, they are asked to provide an example of a cellular process which is not an activity, or a cellular activity which is not a process.

4. $C_{(1-20)}$tetraaminoalkyl is impossible, since four aminos will require at least two carbons. The traverse is mistaken. This is a moiety, so one of its bonds is used for attachment. That leaves only three bonds left for the amino substituents. If applicants disagree, they are invited to draw this substituent without the use of a 5 bonded carbon.
5. The scope of claims 23 and 24 is unclear. For most cytokines, so little is known that it is unclear which category, if any, the cytokine belong in. The public would be forced to unduly experiment to determine which category a given cytokine belonged in. The traverse is unpersuasive. The determination of the properties of a cytokine is a major undertaking, and for the great majority, virtually nothing is known. Determining that a given cytokine does not fall into claim 23 or claim 24 would take extensive research, especially into the cytokine happened to fall into neither category.
6. "Thioalkyl" is not standard nomenclature. Thio as a generic prefix simply indicating the presence of sulfur. It is of course possible that the term refers to HS-alkyl-, which is properly called the mercaptoalkyl group. It is also possible that it is intended to refer to the alkyl-S- group, which is properly called the alkylthio group. It could even possibly refer to the replacement of a carbon in an alkyl with a Sulfur, e.g. CH_3-S-CH_2- or possibly the sulfur could be a double bonded substituent rather than a single bonded one, e.g. CH_3-C(=S)-CH_2- This specification gives no clear evidence as to

which of these plausible choices was originally intended, as the extensive list of definitions does not cover this. The traverse is unpersuasive. Applicants state "it is an alkyl containing a sulfur atom." That is impossible. An alkyl cannot contain a S atom. Alkyl is a group of the formula $-C_nH_{2n+1}$, as is set forth in any dictionary, and thus does not contain a Sulfur. Alkyl might be connected via a S atom, it might be substituted by =S or by –SH, etc, but alkyl itself does not contain S.

Claims 1, 2, 18-37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

A. The third structural formula in claim 1 lacks description in the specification. This is a generic formula where R_4 is absent. No such formula exists in the specification, nor does the definition of R_4 include that option. Although there are a few such species present, that does not provide description for the genus itself, only the species themselves. The traverse is unpersuasive. One of ordinary skill in the art is not going to have "recognized" that a structure that clearly depicts R4 is present actually has R4 as absent. The R4, and the bond to the R4 are not depicted as optional. Therefore, one of ordinary skill in the art would understand that the in that structure, the option of there being a double bond to the N cannot exist for that bond, although it can exist for other bonds in the ring. The additional species that applicants point to simply do not fall within the genus.

Claims 10, 11, 14, 15, 17 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for one isomer, does not reasonably provide

enablement for the other isomer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

These species are not embraced by the generic formula for reason set forth in point A above. Testing appears showing species to be active (thereby giving a utility), but the testing is done only on one isomer, not the other. Limitation to the tested isomer will resolve the matter. The traverse is unpersuasive. The fact that these are not dependent on claim 1 is not the problem --- the issue here is not improper dependence. The issue is that these compounds have no ascribed utility, since the utility is tied to a formula which requires that R4 be present. The tested isomers do not need an ascribed utility, since the testing gives them a utility, but the isomers not tested have not utility to rely upon.

Claims 1-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for other forms, does not reasonably provide enablement for solvates. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The claims are drawn to solvates. But the numerous examples presented all failed to produce a solvate. These cannot be simply willed into existence. As was stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 "The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there is no evidence that such compounds exist... the examples of the '881 patent do not produce the postulated

compounds... there is ... no evidence that such compounds even exist." Hence, applicants must show that solvates can be made, or limit the claims accordingly.

With regard to *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190, the Court held lack of enablement because the disclosed procedures in the specification did not even produce the claimed compounds. That is exactly the case here as well. There are a number of examples reported; not one of them produced a solvate. Applicants state, "The formation of a solvate is within the skill of a person having ordinary skill in the art." One skilled in the art knows that solvates are prepared by exposing the compound to solvent (e.g. by preparing in the presence of solvent) and then isolating the solid. If the compound inherently forms solvates, then one will get a solvate; if not, one will not. That is, some compounds form solvates; some do not. These compounds, judging by the evidence of the specification, are in the latter category. The specification teaches no methods for overcoming this deficiency, i.e. to force a compound, which does not naturally form one, to form a solvate. The specification does not even seem to be aware of the problem. The remarks do not state how to do this, nor does the examiner know of any such technique. The reference is noted, but as the remarks state, it is directed to what a solvate is, not on how to force a compound to form a solvate if it does not naturally form one.

The traverse is unpersuasive. Applicants ask, "What evidence?" As stated above: "the numerous examples presented all failed to produce a solvate." All the examples failed to produce it, exactly as was the case in *Morton*. As for what one of ordinary skill in the art knows, that is exactly the point. One of ordinary skill in the art knows that the method is to expose the compound to the solvent. But since that never worked in all the

examples, it is clear that these compounds simply do not form solvates. The specification teaches no other technique, nor does one of ordinary skill in the art know of one.

Claims 19-25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Pursuant to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue"; see *In re Vaeck*, 20 USPQ2d 1438, 1444. The analysis is as follows:

(1) Breadth of claims:

a) Scope of method. The scope is colossal. It covers inhibiting any activity mediated by any cytokine, without further limitation (see page 20, lines 27-30). It thus probably covers most normal cellular processes and probably covers most diseases, and possibly virtually all diseases and cellular processes.

Cytokines are extraordinarily diverse in their structure and function. The term cytokine is used as a generic name for a diverse group of soluble proteins and peptides

which act as humoral regulators and which, either under normal or pathological conditions, modulate the functional activities of individual cells and tissues. These proteins also mediate interactions between cells directly and regulate processes taking place in the extracellular environment.

As for structure, most Cytokines are unrelated in terms of sequence.

Some attempts have been made to organize cytokines along lines of function, which show the tremendous variety of what is covered by "cytokine". For example, one category is chemokines, a generic name given to a family of pro-inflammatory activation-inducible Cytokines. These include a) SIS family such as SIS-alpha, SIS-gamma and SIS-epsilon, b) SIG family including JE, KC, MGSA (melanoma growth stimulatory activity), PF4 (platelet factor-4), PBP (platelet basic protein), LDCF (lymphocyte-derived chemotactic factor), RANTES, and SMC-CF, c) SCY family including SCY A1, SCY A2, SCY A3, SCY A4, SCY A5, SCY A6, SCY A7, SCY A8, SCY A9, SCY A10, SCY A11, SCY A12, SCYA13, SCY A14, SCY A15, SCY A16, SCY A17, SCY A18, SCY A19, SCY A20, SCY A21, SCY A22, SCY A23, SCY A24, SCY A25, SCY A26 and many others as well.

Another category is Motogenic cytokines, a category Cytokines that influence the motility and migration of cells in ways other than affected by chemotactic processes. The collective term is an functional definition and there is no structural basis that would allow different factors to be classified as motogenic cytokines. Examples include AAMP (Angio-associated migratory cell protein), Adrenomedullin, AMF (autocrine motility factor), ATX (autotaxin), B16-F1 melanoma autocrine motility factor, DF (dissociation factor), Epitaxin, FDMF (fibroblast-derived motility factor), FMSF (fibroblast motility-

stimulating factor) ISF (invasion stimulating factor), Ladsin, Monocyte-derived scattering factor, MSF (migration stimulating factor), PDMF (pancreatic cancer-derived motility factor), SF (scatter factor), SFL (scatter factor-like), and Vitronectin.

Another category is the B-cell growth factor (BCGF), which includes CD23, IL1, IL2, IL4, IL5, IL6, IFN-gamma, TNF-alpha and TNF-beta.

Another type are the colony stimulating factors, which regulate white blood cell production and orchestrate the control of the growth and differentiation of bone marrow progenitor cells. These include M-CSF (macrophage-specific), G-CSF (granulocyte-specific), GM-CSF (macrophage/granulocyte-specific), IL3 (multifunctional), IL-7 and Stem Cell Factor (SCF) and MEG-CSA (megakaryocyte-specific).

A large category of cytokines is the angiogenisis factors, which include aFGF, ANF, Angiogenin, Angiotropin, AtT20-ECGF, B61, bFGF, CAM-RF, ChDI, CLAF, ECGF, ECI, EDMF, EGF, EMAP, Neurothelin, Endostatin, Endothelial cell growth inhibitor, Endothelial cell-viability maintaining factor, Epo, FGF-5, IGF-2, HBNF, HGF, HUAF, IFN-gamma, IL1, K-FGF, LIF, MD-ECI, MECIF, Oncostatin M, PD-ECGF, PDGF, PF4, PlGF, Prolactin, TNF-alpha, TNF-beta, Transferrin, VEGF, and others.

There are many, many other cytokines, including IL8, IL9, IL10, IL11, IL12, IL-13, IL-14, IP-10, GRO, and 9E3.

b) Scope of compounds employed. In addition, the scope of the compounds themselves is very large. There are four variables each with a substantial number of choices for what these variables can be. Moreover, many of these choices are themselves very broad, such as "heterocyclic". Claim 1 and claim 37 each cover billions of compounds.

(2) The nature of the invention and predictability in the art: The invention is directed toward the action of cytokines and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(3) Direction or Guidance: That provided is very limited value, except to make clear what a broad range of disorders is involved. Page 10-11 provides a immense list of disorders, including some very broad categories such as "Inflammatory diseases or disorders" (of which there are hundreds), and "autoimmune diseases" The dosage range information is as broad as a million fold range (page 42 line 32) and is generic as to the particular disease. That is, it is not linked to any particular disorder.

(4) State of the Prior Art. So far as the examiner is aware, pyridopyrimidine triones have not been used as cytokine regulatory pharmaceuticals. In fact, the entire area of agents designed to regulate cytokines is extremely new, although it is quite possible that some medicines operate that way without that being understood at the time the medicine was first used. Almost all Cytokines are pleiotropic effectors showing multiple biological activities. In addition, multiple cytokines often have overlapping activities and a single cell frequently interacts with multiple cytokines with seemingly identical responses (cross-talk). One of the consequences of this functional overlap is the observation that one factor may frequently functionally replace another factor altogether or at least partially compensate for the lack of another factor. Since most Cytokines have ubiquitous biological activities, their physiologic significance as normal regulators of

physiology is often difficult to assess. The activities of cytokines as a group are extremely complex. Many Cytokines show stimulating or inhibitory activities and may synergize or antagonize also the actions of other factors. A single cytokine may elicit reactions also under certain circumstances which are the reverse of those shown under other circumstances. The type, the duration, and also the extent of cellular activities induced by a particular cytokine can be influenced considerably by the micro-environment of a cell, depending, for example, on the growth state of the cells (sparse or confluent), the type of neighboring cells, cytokine concentrations, the combination of other Cytokines present at the same time, and even on the temporal sequence of several Cytokines acting on the same cell. The responses elicited by Cytokines are therefore contextual and the "informational content", i.e. the intrinsic activities of a given cytokine may vary with conditions.

(5) Working Examples: Example 12 and both examples 11 show that most (but not all) of the compounds tested suppress IL-4 or IL-12 signaling, or both. These are just a tiny portion of the cytokines embraced, and these examples do not demonstrate that these compounds have any *in vivo* properties, as these are *in vitro* tests.

(6) Skill of those in the art: The skill level in the art is low, relative to the complexity of task (see point 4 above). In general Cytokines act on a wider spectrum of target cells even than hormones and, unlike hormones, Cytokines are not produced by specialized cells which are organized in specialized glands, i.e. there is not a single organ source for these mediators. The fact that cytokines are secreted proteins also means that the sites of their expression does not necessarily predict the sites at which they exert their biological function. Most cytokines are of unknown, or little known, function. There is

no clear idea how many cytokines there are, as new ones are being discovered all the time. Except for a very few, regulation of the cytokines is a very poorly understood area. (7) The quantity of experimentation needed: Extensive experimentation will be needed; see point 4. This is in part because of the vast scope and complexity of this area. More extensive experimentation than normal is needed because it is already established for at least one cytokine (α-TNF, one of the most extensively studied cytokines) that sometimes suppressing it makes matters worse when one would have expected better. That is, Tuberculosis and MS clearly have α-TNF involvement, but the α-TNF antagonist Remicade has been shown to make matters worse for these! Likewise, while α-TNF has a role in congestive heart failure, patients with CHF are now told to avoid using Remicade because testing showed it to be worse than placebo. The amount of experimentation needed is greater in part because of the fact that it appears that in many cases, suppression of one cytokine simply means that another cytokine will take up the slack.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

The traverse is unpersuasive. Applicants begin by treating this as a rejection under 35 USC 112, paragraph 2. They conclude "Any person skill in the art would have understood the scope of the claim." But that is not the problem alleged. Claim 19's scope

is clear: it covers any activity mediated by any cytokine. Since most cellular activities are mediated by cytokines, this in fact covers most biological activities of the cell.

Applicants initially and in point 4 ask for evidence to support the examiner's characterization of cytokines. This information is known to one of ordinary skill in the art, and applicants have not disputed its accuracy. There is cited the Cytokines, http://home.attbi.com/~bkrentzman/misc/how.things.work/dna.transcription/cytokines.html reference, which states in part, "Today the term cytokine is used as a generic name for a diverse group of soluble proteins and peptides which act as humoral regulators ... and which, either under normal or pathological conditions, modulate the functional activities of individual cells and tissues. These proteins also mediate interactions between cells directly and regulate processes taking place in the extracellular environment ...Some cytokines also behave like classical hormones in that they act at a systemic level, affecting, for example, biological phenomena such as inflammation , systemic inflammatory response syndrome , and acute phase reaction , wound healing , and the neuroimmune network . In general, cytokines act on a wider spectrum of target cells than hormones... cytokines are not produced by specialized cells which are organized in specialized glands, i.e. there is not a single organ source for these mediators. The fact that cytokines are secreted proteins also means that the sites of their expression does not necessarily predict the sites at which they exert their biological function...Most cytokines were detected initially in functional tests in vitro as biochemically undefined activities or as distinct factors with distinct biological activities...One should be aware of the fact that at this moment in time *the relevance of many in vitro activities of cytokines to their endogenous functions within an intact*

organism is not clearly defined. Almost all cytokines are pleiotropic effectors showing multiple biological activities. In addition, multiple cytokines often have overlapping activities and a single cell frequently interacts with multiple cytokines with seemingly identical responses (cross-talk). One of the consequences of this functional overlap is the observation that one factor may frequently functionally replace another factor altogether or at least partially compensate for the lack of another factor. Since *most cytokines have ubiquitous biological activities*, their physiologic significance as normal regulators of physiology is often difficult to assess...Many cytokines show stimulating or inhibitory activities and may synergise or antagonize also the actions of other factors. *A single cytokine may elicit reactions also under certain circumstances which are the reverse of those shown under other circumstances.* The type, the duration, and also the extent of cellular activities induced by a particular cytokine can be influenced considerably by the micro-environment of a cell, depending, for example, on the growth state of the cells (sparse or confluent), the type of neighboring cells, cytokine concentrations, the combination of other cytokines present at the same time, and even on the temporal sequence of several cytokines acting on the same cell. Under such circumstances combinatorial effects thus allow a single cytokine to transmit diverse signals to different subsets of cells.... The responses elicited by cytokines are therefore contextual and the "informational content", i.e. the intrinsic activities of a given cytokine may vary with conditions. Although a variety of cytokines are known to share at least some biological effects the observations that single cells usually show different patterns of gene expression in response to different cytokines can be taken as evidence for the existence of cytokine receptor-specific signal transduction pathways....The processes

responsible for the regulation of cytokines are not well understood. ...Frequently one observes a hierarchical order of cytokine actions with some early Cytokines preactivating cells so that they then can respond to late-acting cytokines ...A close examination of the physiological and pathological effects of the regulated or deregulated ... expression of cytokines in complex organisms has shown that *these mediators are involved in virtually all general systemic reactions of an organism ... including such important processes as the regulation of immune responses ..., inflammatory processes ... hematopoiesis ... and wound healing...Cytokines are important mediators involved in embryogenesis and organ development ... and their activities in these processes may differ from those observed postnatally. In addition they play a key role in neuroimmunological, neuroendocrinological, and neuroregulatory processes ... Cytokines are important positive or negative regulators of mitosis ... differentiation, migration ... cell survival and cell death .. and transformation ...* It has been shown that a number of viral infectious agents exploit the cytokine repertoire of organisms to evade immune responses of the host. Virus-encoded factors ... appear to affect the activities of cytokines in at least four different ways... Cytokines themselves rarely are related closely among each other in terms of primary Sequences..." Emphasis added. This clearly supports the examiner's statements. In addition, there is cited the Chemokines, Horst Ibelgaufts' COPE: Cytokines Online Pathfinder Encyclopaedia, http://www.copewithcytokines.de/cope.cgi?001668 reference. This covers just a single category of cytokines, the chemokines. This shows that there are literally hundreds of chemokines just in this category alone.

With regard to point 1, applicants state that "the claims are not so broad." This is absurd. They probably cover virtually all disorders. If applicants disagree, they are invited to name some major diseases which do not fall within claim 1. Similarly, applicants state, "The cytokine mediates cellular activity or it does not." This is mistaken. All cytokines mediate cellular activity. If it does not, it would not be a cytokine.

With regard to point 2, applicants state "...it is not evidence that the physiological activity is a factor in the method of base claim 19." This makes no sense. The claim says "activity mediated by a cytokine." Those activities are physiological. Surely applicants are not arguing that the activity of a cytokine is non- physiological.

With regard to point 3, applicants argue that there is "reasonable guidance" and "approximate dosage ranges." But the dosage range is presented without any regard to what disease is involved. These are extremely diverse. For example, the specification says, "Inflammatory diseases or disorders". This includes just as examples, Otitis media, Cystitis , Blepharitis, Dacryocystitis, Preseptal cellulitis, Cholecystitis, gout, Sinusitis Pharyngitis , Osteomyelitis, Dacryoadenitis, Conjunctivitis, Rheumatoid arthritis, Pneumonia Adult (or Acute) Respiratory Distress Syndrome (ARDS), Chronic bronchitis, Acute bronchitis, Asthma, Myocarditis, Glossitis, Meningitis, Myelitis, Dactylitis, Inclusion body myositis, Encephalitis, Hepatitis, Hemorrhoids, frostbite injury, bacterial meningitis, acute airway inflammation, allograft rejection, hemorrhagic shock, septic shock, ischemia reperfusion injuries, Urethritis, eruption of teeth in a child (teething), Inflammation of the nails, Bright's disease (or glomerulonephritis), Thyroiditis, Regional enteritis (Crohn's disease or ileitis), bronchiolitis, alveolitis,

vasculitis, idiopathic pulmonary fibrosis, bronchiolitis obliterans, histiocytosis X, chronic eosinophilic pneumonia, granulomatous vasculitis, Goodpasture's syndrome, pulmonary alveolar proteinosis, asbestosis, coal worker's pneumoconiosis, silicosis, byssinosis, aluminosis, anthracosis, asbestosis, chalicosis, siderosis, tabacosis, hypersensitivity pneumonitis, Pulmonary Sarcoidosis Bronchiectasis, Stomatitis, mucositis, aphthous ulcers, Acute Necrotizing Ulcerative Gingivitis i.e. "trench mouth", Lichen Planus, Rhinitis, Wegener's Granulomatosis, Pancreatitis, Neuroretinitis, River blindness, scleritis, episcleritis, choroiditis, uveitis, Atrophic gastritis, Erosive (hemorrhagic) gastritis, appendicitis, sunburn, reaction to ticks or bee string, acute allergic contact dermatitis (such as poison ivy), pili incarnati, Acne, Prostatitis, Cystic fibrosis (CF) and many more.

With regard to point 4, the examiner has said, "So far as the examiner is aware, pyridopyrimidine triones have not been used as cytokine regulatory pharmaceuticals." Obviously, a negative cannot be proven; it applicants disagree, they are invited to provide a counterexample.

With regard to point 5, applicants refer to "every conceivable cytokine known in the art." The examiner has not made such a requirement. But these two cannot be deemed representative of a group of hundreds of diverse cytokines, and as noted, do not demonstrate in vivo properties.

With regard to point 6, applicants response is in terms of this being a 35 USC 112, paragraph 2 rejection, which it is not. Further the difficulty of establishing what activities are affected in what ways is attested to by the above quotation, and is well known to one of ordinary skill in the art.

With regard to point 7, the National Psoriasis Foundation "News & Notices" http://www.psoriasis.org/enbrel.approval.jan02.htm reference says flatly, "People with known multiple sclerosis should not take Enbrel." That is clear evidence that the prior art teaches that inhibitors of α-TNF make matters worse, not better. A similar warning appears for TB. Applicants response is simply not understood. Applicants state, "If α-TNF activity is inhibited..." Why does applicant state, "If"? Surely applicants are aware that α-TNF is a cytokine, and indeed, is one of the most important. This claim thus reads on inhibiting α-TNF. The point here is that while based on the understanding of the effects of α-TNF, one would expect treatment with an inhibitor of α-TNF to make matters better for MS, but in fact, it made matters worse. Despite all the research done, more experimentation was clearly needed. Applicants state, "The fact that suppressing α-TNF may make a condition worse is immaterial to a claim...." Why is that immaterial? How is something to be used if it makes the condition worse? The reference "Centocor Places Congestive Heart Failure Clinical Program On Hold" http://www.jnj.com/news/jnj_news/20020329_0810.htm is cited for support for the statement about CHF, and note the additional statement that "other recent trials have failed to demonstrate that agents that bind TNF can improve the clinical course in these patients." This shows that even the extensive experimentation that has been done for use of one compound for inhibiting one activity – CHF --- was not sufficient. This shows that extensive experimentation is needed.

Claim Objections

Claims 4-7 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. There is no provision in claim 37 for such substituents. For example, claim 4 lists carboxyl or heterocyclic, yet none of the claim 37 choices have carboxyl or heterocycle as a substituent for R_2 or R_3.

The traverse is unpersuasive. Applicants are believed to be misreading claim 37. The only choices for R2 and R3 are those listed in the claim, and this does not provide for the further substititon by e.g. carboxyl. The "substituted" in the first line refers to the substituents already present, that is, for example, the 4-chloropentyl has the Cl substituent. Noe that the page 32 language, which applicants have pointed to, does not provide for further substitution. If applicants disagree, theyare asked to show where the specification would provide for descriptive support for 4-chloropentyl substituted by carboxyl. Page 32 does not have it.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Berch whose telephone number is 703-308-4718. The examiner can normally be reached on M-F 7:15 - 3:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mukund Shah can be reached on 308-4716. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 708-308-1235.

Mark L. Berch

Primary Examiner

Art Unit 1624

October 25, 2002